Inter-SPORE Prostate Biomarkers Study: Addressing Prognosis and Pilot for NBN

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Specialized Programs
of Research Excellence

Overview of Presentation

- **Motivation for the Inter-SPORE Prostate Biomarkers Study (IPBS)**
- **IPBS conceptual parameters and study design**
- **Common requirements of IPBS and NBN**
- **Features of NBN to be piloted in IPBS**

The Biomarker Conundrum for Prostate Ca

- **PubMed Search on “prostate cancer” and “prognostic” and “biomarker” yields 2031 hits**

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- **Number of molecular biomarkers routinely used by urologists for prognosis: 1 (PSA)**
- **Why haven't prognostic biomarkers lived up to their promise?**

Why haven't prognostic biomarker studies led to translation?

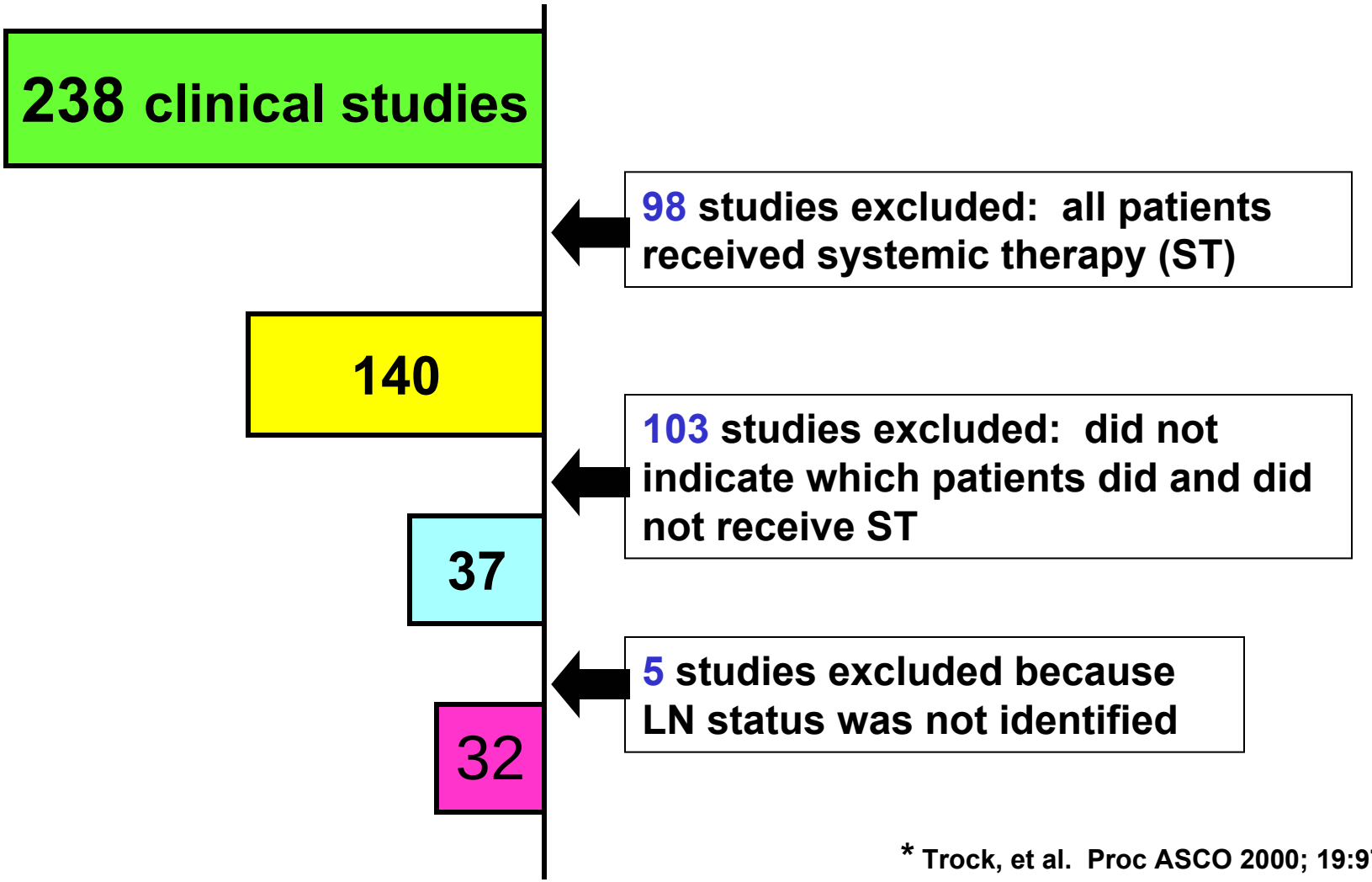
- prognostic vs. predictive role of a biomarker
- variability in patient populations (treatment, risk level, convenience samples)
- assays not standardized or optimized
- inadequate study power or statistical analysis
- studies usually based on a single institution

Common Underlying Goals of IPBS and NBN

- **Goal of the IPBS**: rigorous prospective validation of promising biomarkers using standardized methods, sustainable infrastructure and optimized design (control pre-analytical and analytical error)

- **Goal of the NBN**: a "best-practices"-based resource to manage standardized collection, processing, storage and disbursement of high-quality biospecimens and linked data to support and reduce variability in translational research (control pre-analytical error)

A Cautionary Tale:
c-erbB-2 and Breast Cancer Prognosis*

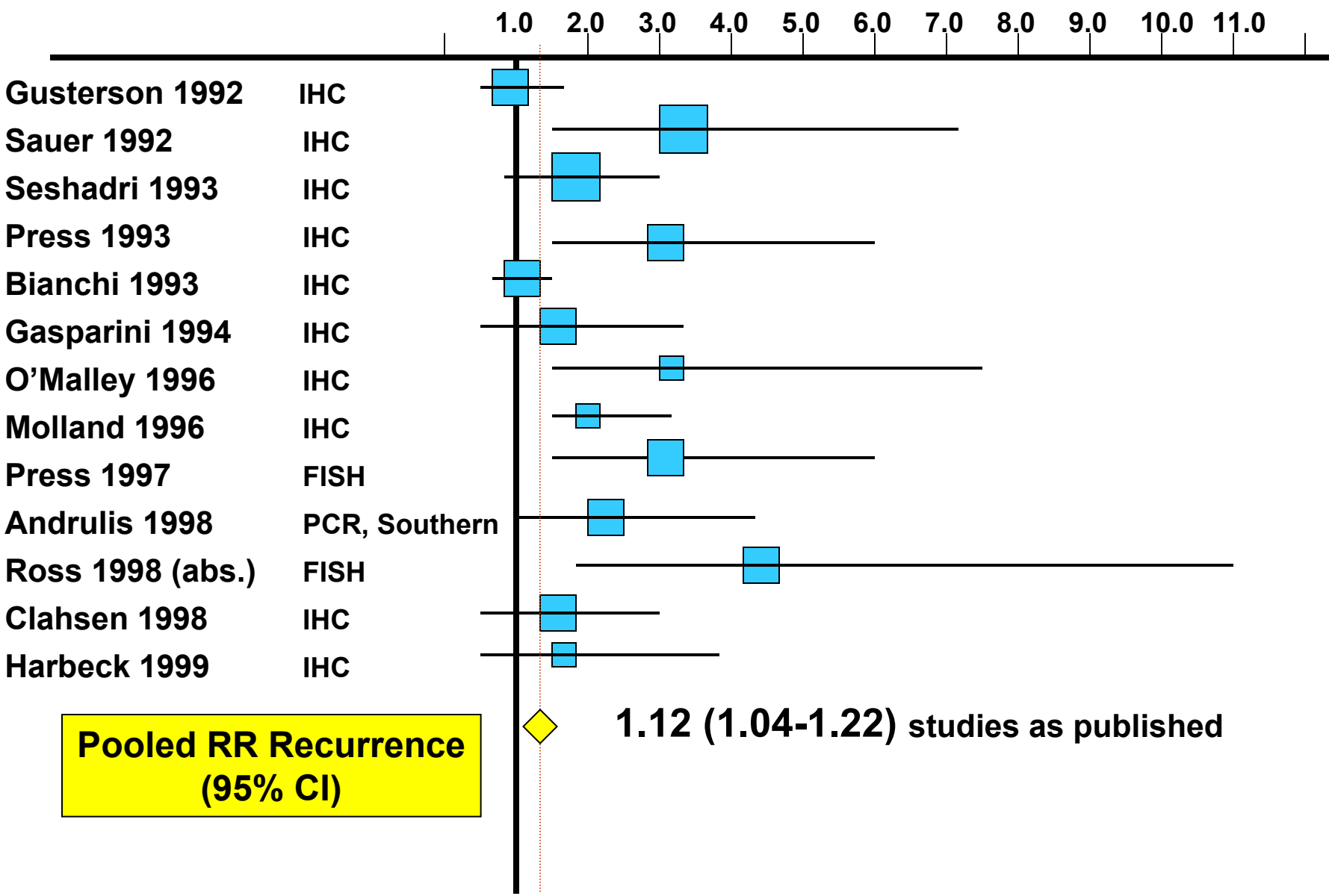


* Trock, et al. Proc ASCO 2000; 19:97a.

L/N Negative

Relative Risk of RECURRENCE

c-erbB-2 Better ⟷ c-erbB-2 Worse



IPBS Research Question

- **Does the biomarker improve upon existing nomograms to predict aggressive cancers that will progress following RRP or XRT?**

- **Selection of biomarkers: Meta-analysis and separate scientific reviews of 14 promising biomarkers resulted in panel of 8 candidates**

Candidate Biomarkers

Prospective Study

- **8q24**
  Mayo Clinic / Jenkins
- **Caveolin 1**
  Baylor / Thompson
- **hK2**
  MSKCC / Lilja, Mayo / Young
- **Ki-67**
  Johns Hopkins / DeMarzo
- **p27**
  UCLA / Reiter, Harvard / Loda

Retrospective Study

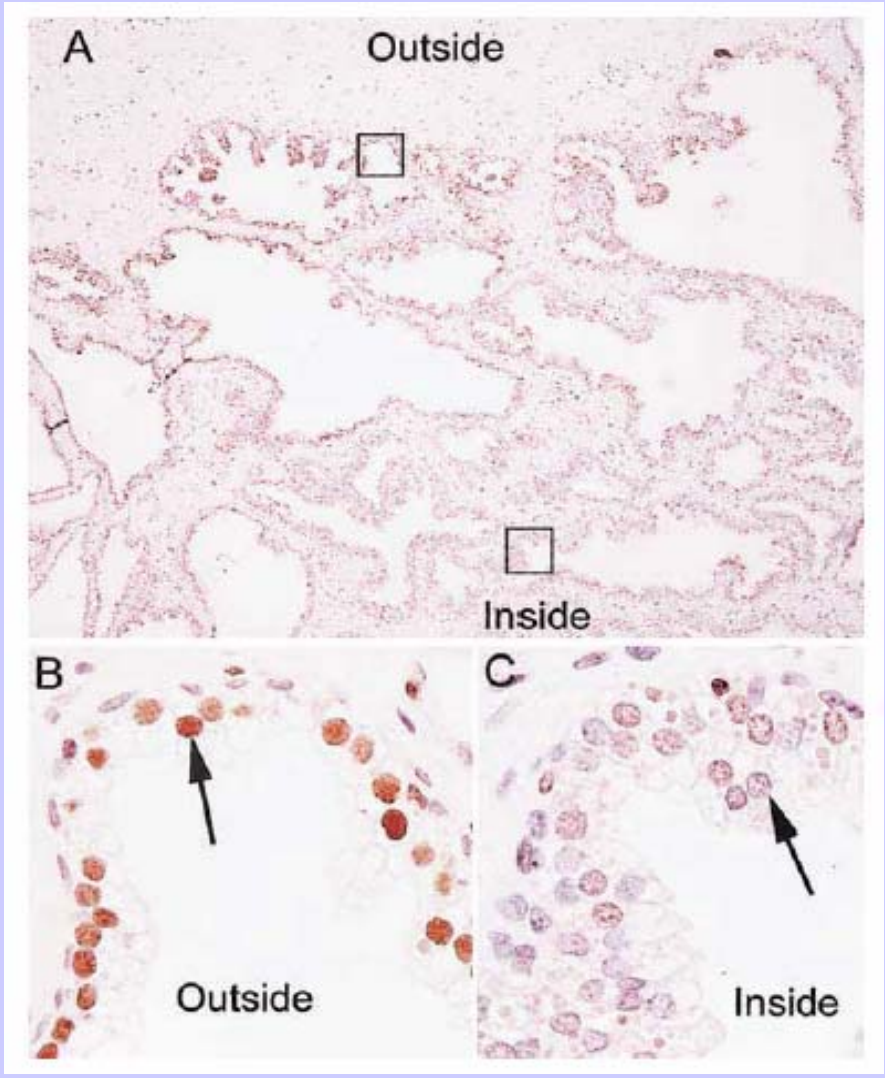
- **EZH2**
  DFCI / Rubin, U-M / Chinnaiyan
- **c-met**
  U Washington / Knudson
- **TGF-β1**
  Northwestern / Lee

Why Do this Study?

- **Improve upon current prognostic classification**
- **Foundation for accelerated discovery and development of new biomarkers**
- **Why a prospective study?**
  - **rigorous validation of prognostic markers hasn't been done!**
  - **standardized methods (pre-analytical error)**
  - **quality control**
  - **appropriate patient population**
  - **uniform determination of outcomes**
  - **patients who progress can enter clinical trials**
- **Why study these "old" biomarkers?**
  - **few biomarkers have good evidence for prognostic role**
  - **clinical usage requires methodological stringency**

Effect of inadequate fixation time on p27 staining

(DeMarzo, et al. Human Pathol 2002)

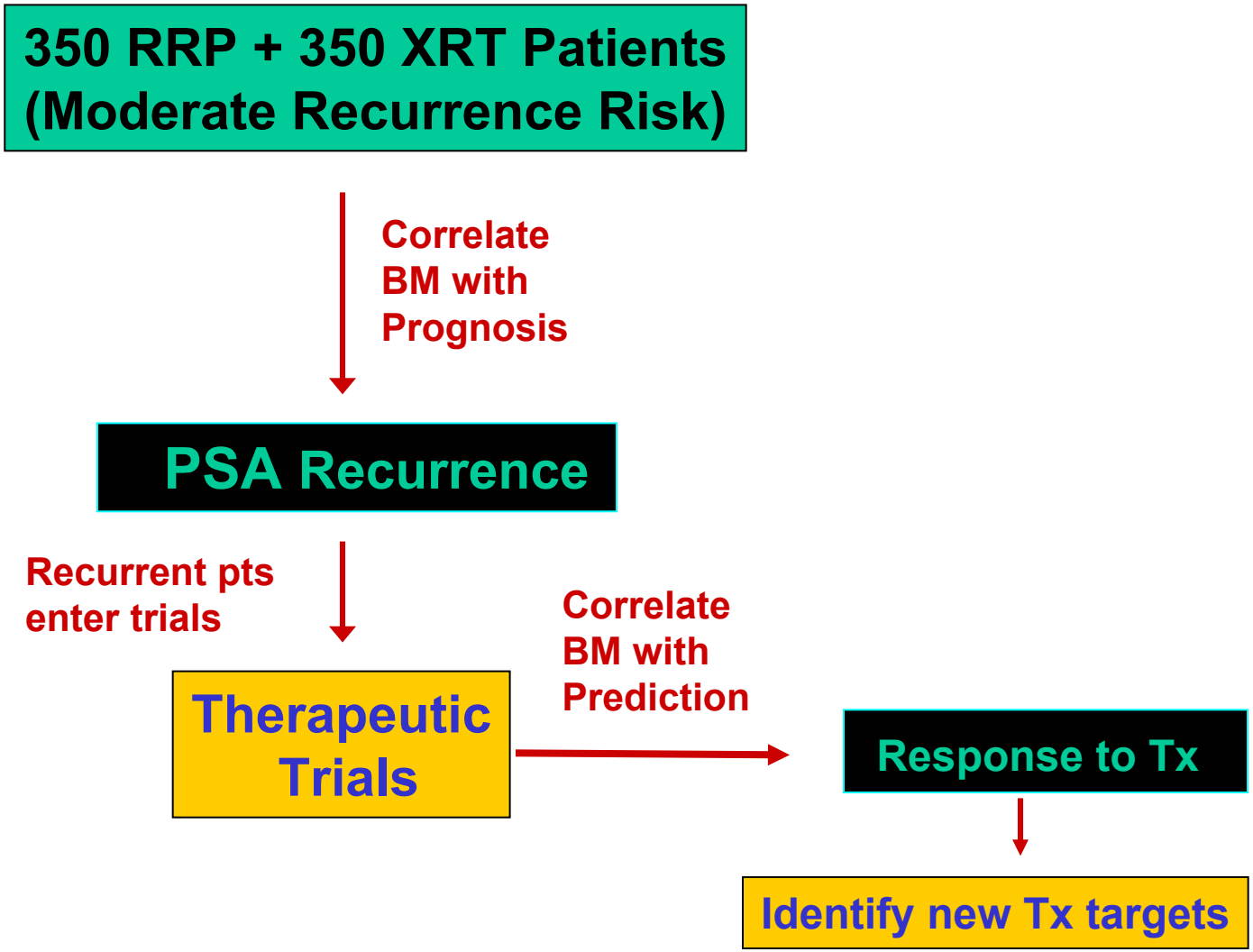


Prospective Biomarkers (BM) Study

350 RRP + 350 XRT Patients
(Moderate Recurrence Risk)

PSA Recurrence

Prospective Biomarkers (BM) Study



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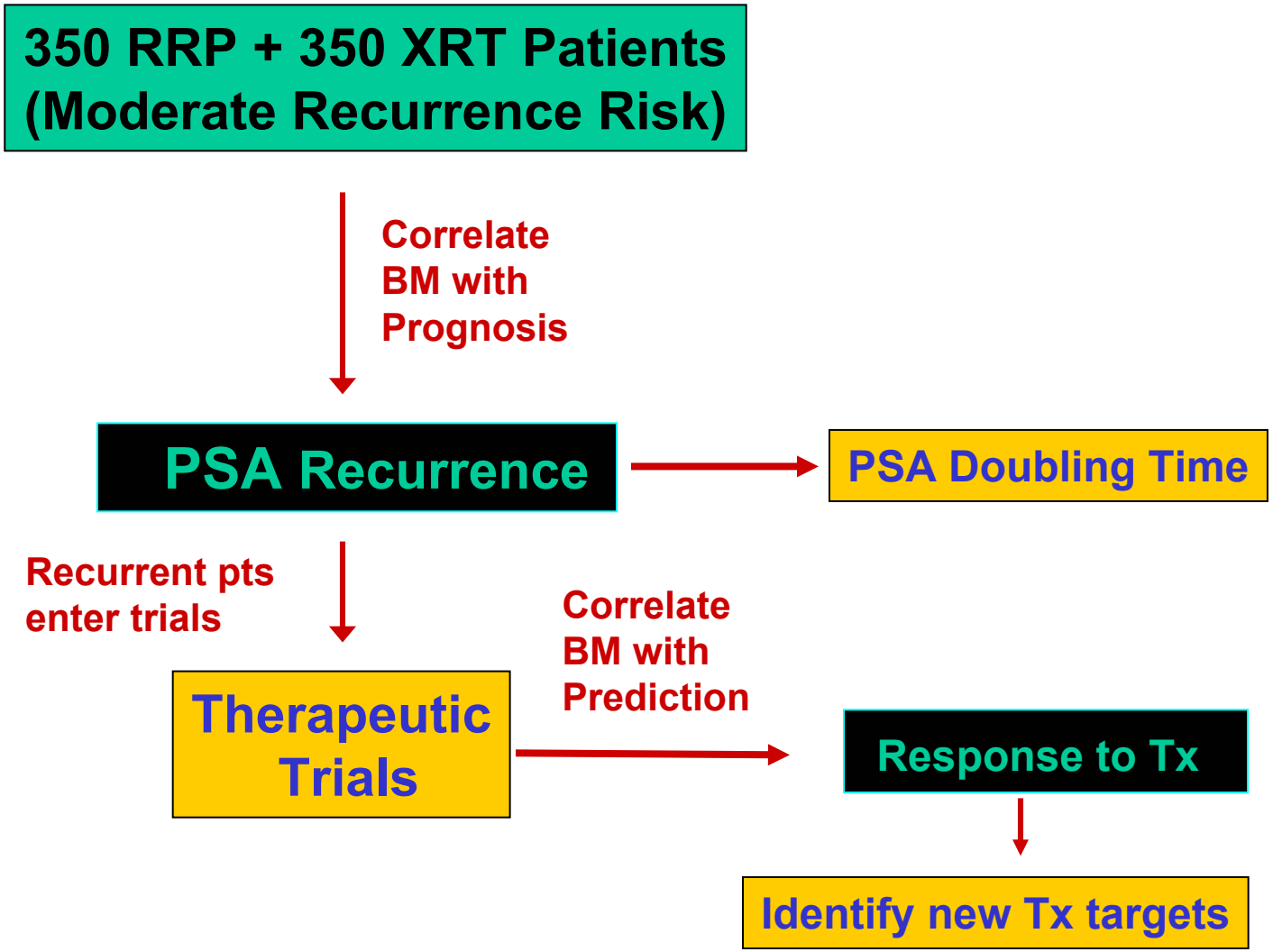
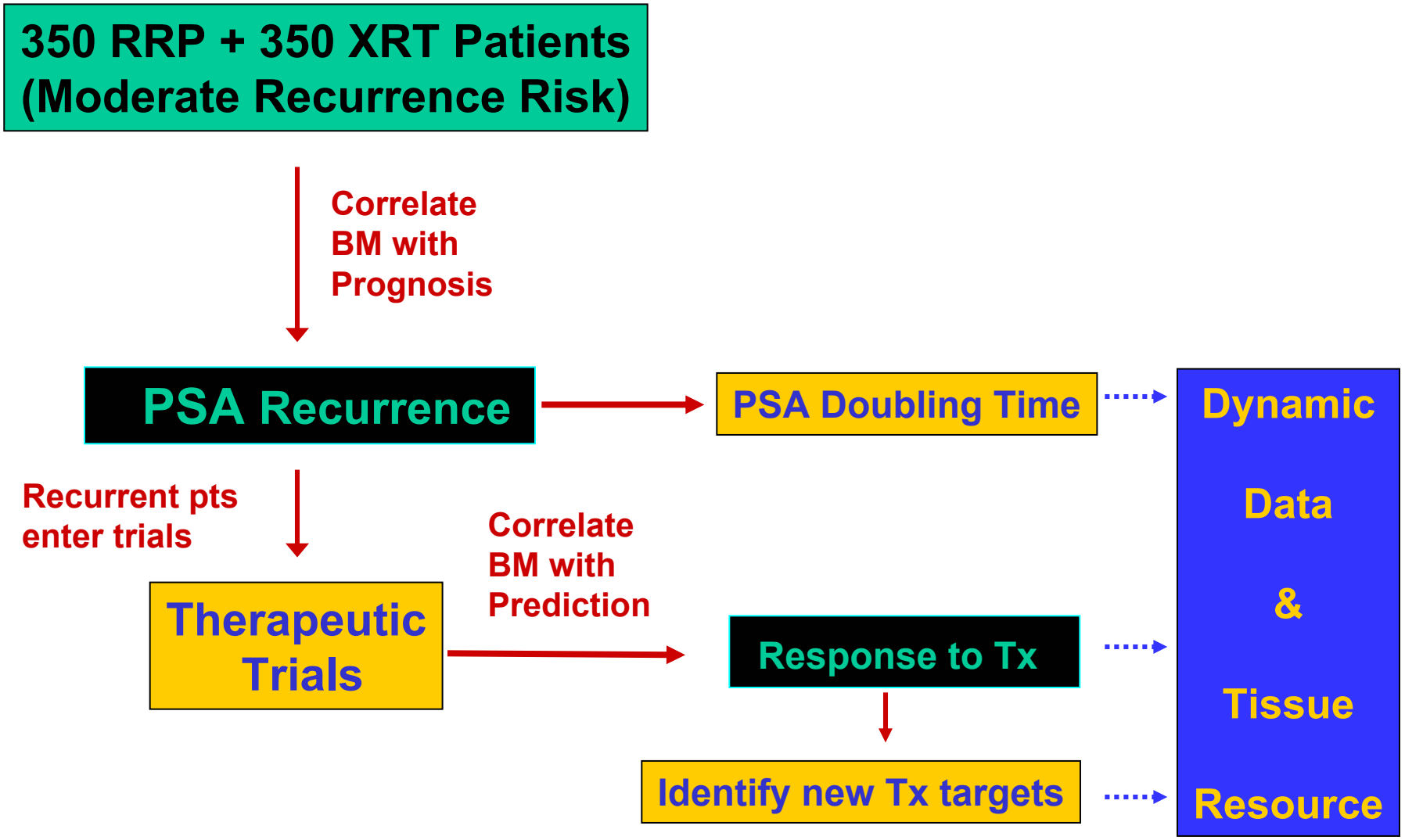
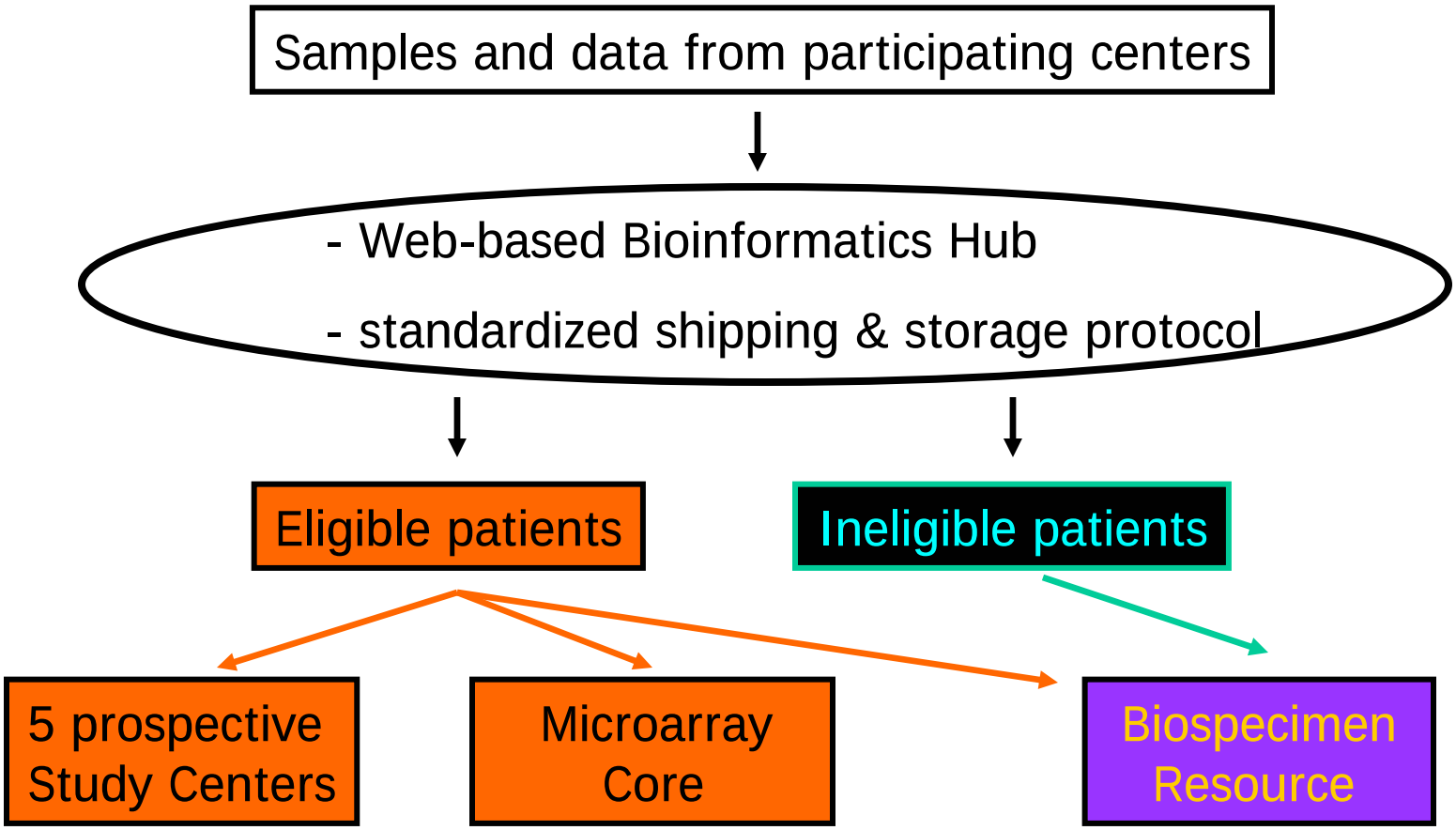
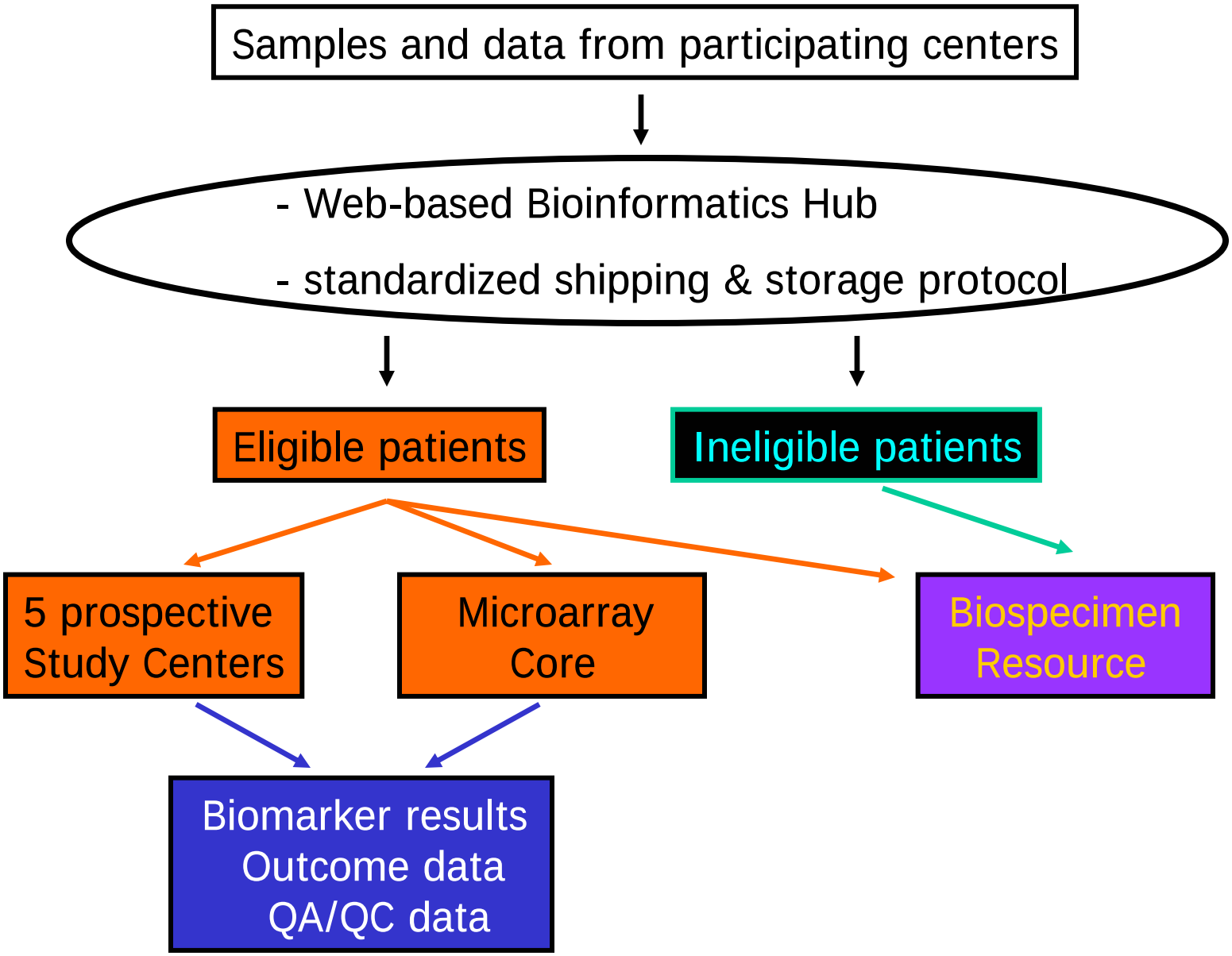


"Value added" from Biomarkers Study




Samples and data from participating centers
- Web-based Bioinformatics Hub
- standardized shipping & storage protocol
Eligible patients
Ineligible patients
5 prospective Study Centers
Microarray Core
Biospecimen Resource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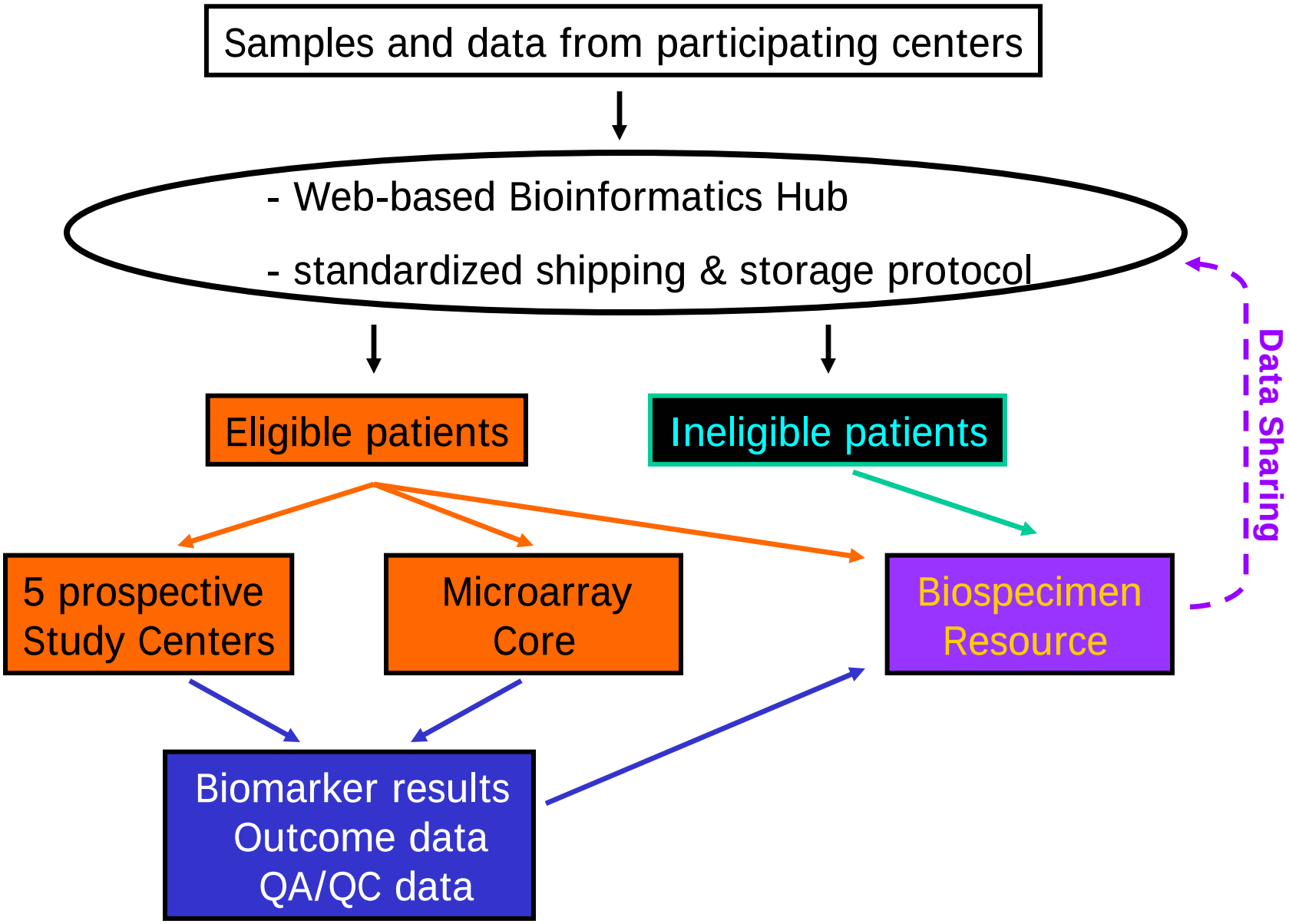
Outcome data
QA/QC data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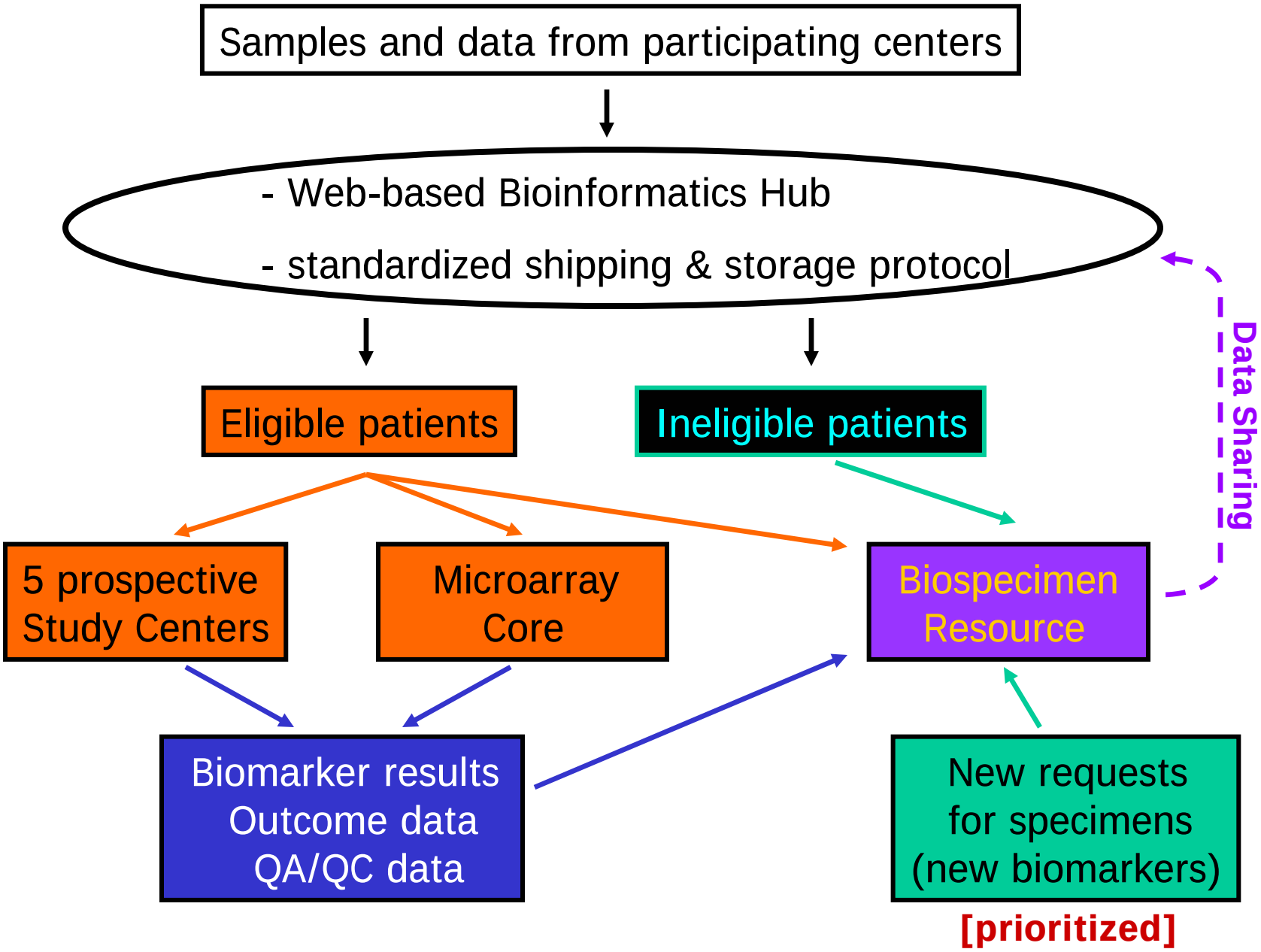
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New requests for specimens (new biomarkers)
[prioritized]

Common Requirements for IPBS and NBN

- Dispersed network of tissue contributors and users
- Standardized methods where possible; identify tolerances when standardization not possible
- Emphasis on annotation of specimens
- Flexible, scalable bioinformatics system
  - Web-based, prioritization of access, password protected
  - CDEs, minimum data set for each sample
- Integrated QA/QC
  - data tracking, edit checks, random sample review
  - shipping manifests, verification of receipt
  - H&E, pathology report accompany tissue
  - query investigators about biomarker assay results

Common Features of IPBS and NBN (cont'd)

- **Prioritize access to specimens**
  - **IPBS Tissue Resource Oversight Committee**
  - **users must have IRB-approved protocol**
- **Informed consent, confidentiality**
  - **common consent elements (CCEs), HIPAA compliant**
  - **tiered consent options**
  - **link between specimens and PHI is off-line**
- **Intellectual property**
  - **provider institutions do not retain rights to specimens**
  - **common criteria for licensing, MTAs, authorship**
- **The study will create a dynamic resource that will also support clinical trials, and discovery of new biomarkers**